Remarks

- Claims 1, 4 – 9 are rejected for being unpatentable over Tabuchi, et al., in view of Donovan.

Claims 1, 4 – 9 are Rejected under 35 USC 103(a)

Examiner has rejected Claims 1, 4 – 9 as being unpatentable over Tabuchi, et al., in view of Donovan. Without necessarily acquiescing to the Examiner's arguments, independent Claim 1 has been amended to further recite the active step of "and correlating the administration of ketamine with a reduction in tinnitus and with suppressed or reduced NMDA receptor-mediated aberrant activity of the auditory nerve." The cited art cannot render obvious this step since the cited art in combination does not teach, fairly suggest of render predictable the treatment of tinnitus with ketamine "effective to suppress or reduce NMDA receptor mediated aberrant activity of the auditory nerve." Support for this amendment can be found in the Exemplification section of the pending application. Applicants respectfully traverse this rejection.

The Applicants disagree with the Examiner's reasoning in the finding of obviousness for the pending claim set. The Examiner states:

> The mechanism by which the active ingredient gives the pharmacological effect does not alter the fact that the compound has been previously used to obtain the same pharmacological effect (protection against **ischemic injury** to the cochlea) ... The patient, condition to be treated and the effect are the same. **Emphasis added.** Pending Action, page 3.

Applicants show below that in the present invention and in sharp contrast to the cited art the "patient, condition to be treated and the effect" are not the same. Contrary to the Examiner's assertions, the present invention is not directed towards ischemic injury or hearing loss resulting from such injury, as is taught in Tabuchi.

Ischemia is defined as "an insufficient supply of blood to an organ, usually due to a blocked artery." However, and contrary to the Examiner's assertion, the present invention is not directed towards "protection against ischemic injury to the cochlea." The present invention is limited to the treatment of tinnitus "induced by excitotoxicity" and wherein treatment "suppress[es] or reduce[s] NMDA receptor mediated aberrant activity of the auditory nerve." Excitotoxicity is defined in the art as the pathological process by which nerve cells are damaged and killed by glutamate and similar substances. (www.wikipedia.org/wiki/Excitotoxicity; pending specification paragraph [0012]). NMDA antagonists block receptor binding of glutamate and

similar substances thereby suppressing or reducing NMDA receptor mediated aberrant activity of the auditory nerve. Pending specification, paragraph [0024].

Applicants further submit that the combination of art cited by the Examiner does not teach, fairly suggest or render predictable the presently claimed invention for the following reasons.

Comments on the Tabuchi publication

Applicants submit that the Examiner's assertion that the skilled person in the art based on the teachings of Tabuchi (in view of Donovan) would obtain the same pharmacological effect as in the present invention is incorrect. Tabuchi, et al., describe the protection against hearing loss or protection against ischemic injury to the cochlea and not tinnitus. Therefore, the pharmacological effect of the presently claimed invention as compared to the teachings of Tabuchi is distinct. There is not the slightest hint in the literature in general or in Tabuchi in particular that a successful treatment of hearing loss automatically leads to a successful treatment of tinnitus. In fact, tinnitus is a symptom that may or may not accompany ischemic hearing loss as cochlear ischemia is not automatically inducing tinnitus, and when it does, the tinnitus may just be very short-lived. Reference is made to Applicant's findings that even in case of a severe acute acoustic trauma that is producing a much more profound hearing loss than observed in the Tabuchi et al. model, only a minority of animals developed persisting tinnitus. Tabuchi's assertion that "successful ketamine treatment" was provided relates exclusively to "hearing loss" and not to tinnitus. It is well known in the art that hearing loss triggered by cochlear ischemia is due to metabolic stress and damages particularly on outer hair cells in the cochlea. Accordingly, Tabuchi is seeking to protect hair cells, whereas Applicants are using an NMDA receptor antagonist to modulate a receptor mediated aberrant activity of the auditory nerve – these are two clearly distinct pharmacological targets.

The Examiner makes conclusions on the next logical step that one of skill in the art would take in view of Tabuchi's experiments. Pending Action, page 6. Applicants submit, however, instead of testing ketamine for the treatment of tinnitus, the skilled person would rather have tested one of the many specific nitric oxide inhibitors, dopamine agonists or calcium channel blockers mentioned by Tabuchi. This is due to Tabuchi's speculation that the effects of ketamine may be due to inhibition of nitric oxide release or enhancement of dopamine release. Tabuchi concludes from his findings, that agent MK-801 (another NMDA receptor antagonist) has no protective effect for hearing loss. Therefore, he suggests that any effect observed for

ketamine is triggered via other pathways than NMDA receptor inhibition.[1] Why should a skilled person in view of Tabuchi's disclosure for the treatment of hearing loss, (and not tinnitus) and even further in view of the fact that Tabuchi even suggests another mechanism for ketamine's effect on the treatment of hearing loss (other than its NMDA receptor antagonist properties) conclude that ketamine (by its NMDA receptor antagonistic properties) exerts an anti-tinnitus effect as shown by the present application? The Applicant can not see any scientific reason for the skilled person to test or employ ketamine for the treatment of tinnitus in view of the Tabuchi publication.

Furthermore, it should be emphasized that there was no model available at all in the art at the time of filing of the present application to determine the presence of tinnitus following excitotoxicity. That is also confirmed by the Tabuchi publication, which - as already mentioned above - does not measure the activity of test compounds for the treatment of tinnitus, but rather for the treatment of hearing loss. To further substantiate that argument, it should be noted that there are two forms of tinnitus (as also disclosed in our own application, namely a transitory form (lasting for one day) and a non-transitory form which starts only on day two, after the transitory tinnitus has disappeared). However, ketamine as NMDA receptor antagonist does not exert any effect on the transitory form of tinnitus. As a consequence, the skilled person would have faced the following further difficulties in view of the Tabuchi publication:

(a) The skilled person would not have had any model for testing, the effect of compounds for the treatment of tinnitus following excitotoxicity at the time of filing of the present application. Even if he would have had such a model, he would (b) not have identified ketamine as a successful compound for treating tinnitus, since Tabuchi evaluates (by his model, which is not appropriate for the identification of anti-tinnitus compounds) ketamine properties just up to 4 hours post ischemia. Accordingly, the skilled person would just have measured ketamine's effect for the treatment of the transitory tinnitus form (which would have failed), since ketamine (as outlined above) does not evoke any impact on the transitory tinnitus form.

---

[1] In contrast, the findings of the present invention are based on the NMDA receptor as a target for the treatment of tinnitus.

Comments on the Donovan publication

The Donovan publication is based on a tinnitus concept which is completely distinct from the concept underlying the present application. The Applicants' object is clearly not denervation as postulated by Donovan, (which, by the way, leads to unacceptable hearing loss). To underscore this difference, the present application cites the importance of specifically targeting the NMDA receptor to avoid interfering with normal auditory transmission. In contrast, Donovan is inspired by "inner ear tinnitus treated by section of the auditory nerve" [column 2, lines 47 – 48]. Accordingly, Donovan teaches the "treatment of cochlea synaptic, cochlear nerve dysfunction tinnitus by way of inner ear denervation" [column 9, lines 9 – 14]. This difference between the teachings of the presently pending application and the teachings of Donovan is further emphasized by Donovan at column 9, lines 49-52, 56-65.

Accordingly, Donovan teaches the use of botulinum toxin to bring about therapeutic inner ear denervation as effective treatment of inner ear tinnitus. It goes without saying that Donovan's publication is based on a completely different concept than the present application and there is no reason why the skilled person would have identified ketamine as potential tinnitus curement in view of the Donovan publication. Additionally, it should be noted that botulinum toxin has numerous effects on various neurotransmitters: "... in brain synaptosome preparations botulinum toxin inhibits the release of each of the neurotransmitters acetylcholine, dopamine, norepinephrine, CGRP and glutamate". All of these neurotransmitters also occur in the cochlea. Accordingly, botulinum toxin may target all of them leading to very unspecific effects.

Finally, it should be emphasized that Donovan provides just one example for the treatment of inner ear tinnitus referring to one patient, based on "cochlea nerve dysfunction." There is no indication in the disclosure of Donovan that the tinnitus model was anyhow related to cochlea ischemia or excitotoxicity in general. Another weakness of that single experiment provided by Donovan is that just one single patient was subjected to treatment, even though any skilled person knows that tinnitus "is a complicated indication and not directly measurable without any control group, since tinnitus treatments are known to induce significant placebo effects in humans." Dobie, 2004 (attached).

Combination of Tabuchi and Donovan

Finally, Applicants want to summarize why the skilled person would not have combined the documents of Tabuchi and Donovan. There is almost no common disclosure in Tabuchi, et al., and Donovan which would allow the skilled person to combine both documents. Tabuchi does not even mention tinnitus, botulinum toxin or exocytosis, whereas Donovan does not disclose ischemia, excitotoxicity or NMDA receptors.

Furthermore, Tabuchi refers to "cochlear dysfunction induced by transient ischemia," whereas Donovan refers to "cochlear nerve dysfunction." Insofar, the skilled person is not guided to combine both documents, since "cochlear dysfunction" is distinct from "cochlear nerve dysfunction." Thus a combination of Tabuchi and Donovan would not have been envisaged by the skilled person.

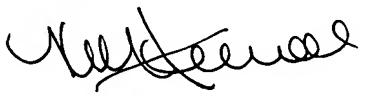
In summary, botulinum toxin (as used by Donovan) blocks neurotransmitter release (glutamate and neuropeptides) at peripheral nerves by disrupting exocytic processes (Dolly and Aoki, 2006, enclosed herewith). Donovan's object is denervation, whereas the object of the present application is clearly specific targeting of NMDA receptor antagonists without interfering with physiological neurotransmission. Donovan in combination with Tabuchi would not have identified ketamine as potential tinnitus treatment, since his model does not rely on excitotoxicity induced tinnitus.

However, and while not necessarily agreeing with the Examiner's arguments or reasoning and while reserving the right to prosecute the same unamended or similar claims in the future, Applicants have amended pending independent Claim 1 to further recite the active step of "and correlating the administration of ketamine with a reduction in tinnitus and with suppressed or reduced NMDA receptor-mediated aberrant activity of the auditory nerve." Support for this amendment can be found in the Exemplification section of the pending application. Since neither Tabuchi nor Donovan, alone or in combination, teach or fairly suggest the involvement of NMDA receptor-mediated aberrant activity of the auditory nerve in tinnitus, Applicants submit that the combination of references cited by the Examiner do not render unpatentable the claimed invention as amended and respectfully request the withdrawal of the rejection and allowance of the claims.

Summary

Applicants respectfully request consideration of the pending specification in view of this Response. Any deficiency or overpayment should be charged or credited to Deposit Account No. 50-4514.

Respectfully submitted,



Kevin M. Farrell
Attorney for Applicant
Registration No. 35,505
(603) 433-6300

Portsmouth, NH
Dated: 12/28/08

P0230119.DOC